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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,763	05/11/2006	Piergiorgio Donati	277219US0PCT	8416

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OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
GUCKER, STEPHEN	

ART UNIT	PAPER NUMBER
1649	

NOTIFICATION DATE	DELIVERY MODE
04/16/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/549,763	DONATI ET AL.	
	Examiner	Art Unit	
	STEPHEN GUCKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *3,16 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-15 and 18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1, 2, 4-15, and 18-29 in the reply filed on 8/15/08 is acknowledged.

2. Claims 3 and 16-17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/15/08.

3. The use of the trademark PLURONIC® has been noted in this application, e.g. pages 16-17 and 42-43. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 9-10 contain the trademark/trade name PLURONIC®. Where a

trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to identify/describe poloxamers, and particularly poloxamer 188 and, accordingly, the identification/description is indefinite.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-2, 6-13, 18-19, and 22-27 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 97/29767 (reference AB on IDS filed 9/19/05; "McNamara"). McNamara discloses a liquid formulation (claim 9) comprising hGH, a most preferably 0.8 - 10 mg/ml (0.08 – 1.0%) polyethylene-polypropylene glycol (PLURONIC® F68) (page 8, lines 24-27), a 20 mM

citrate buffer, a stabilizer (sodium chloride for isotonicity), and a 9mg/ml (0.9%) preservative (benzyl alcohol), at a pH of 5.6. See McNamara at pages 17 and 20-21. The formulation of McNamara may be a sterile pharmaceutical formulation in an airtight sealed container suitable for storage (pages 3-4, 6, 10, lines 13-16 and 26-28, and 11, lines 1-6). Phenol may be used as a preservative (page 10, lines 13-16). The pH may be from about 5 to about 7.5 (page 8, lines 10-12), including pH 6 (Table 2 and claim 9). PLURONIC® is the registered trademark for poloxamer, PLURONIC® F68 is the registered trademark for poloxamer 188.

8. Claims 1-2, 4-13, 18-24, and 26-29 are rejected under 35 U.S.C. 102(e) as being anticipated by US2006/0165733 ("Betz"). Betz discloses a sterile liquid formulation in a storage container for pharmaceutical use (paragraphs [0009], [0016], [0061 – 0062], and [0074]) comprising hGH, sucrose stabilizer (at a concentration up to 30, 50, or 70 mg/ml; paragraph [0042]), 5-100 mM citrate buffer (paragraph [0040]), 0.05 – 4 mg/ml of poloxamer 188 (paragraph [0041]), 2 – 5 mg/ml phenol preservative (paragraph [0039]), at a pH of about 6.1 to about 6.3 (paragraph [0024]). PLURONIC® is the registered trademark for poloxamer, PLURONIC® F68 is the registered trademark for poloxamer 188.

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 2, 4-15, and 18-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Betz in view of US 5,567,677 (reference AA on IDS filed 9/19/05; "Castensson") and further in view of McNamara. The teachings of Betz and McNamara are as set forth in **¶8** and **¶7** above, respectively. Betz does not teach the advantages of lowering the pH of a liquid formulation of hGH below 6.1. Castensson teaches that:

"a large number of reactions can occur under different pH conditions and it is almost impossible to formulate a protein at a particular pH that eliminates all the modification reactions while maintaining high solubility and proper conformation of the protein. Until now a slightly alkaline pH has generally been used by manufacturers to avoid visible particles and to obtain a clear product. In most commercial products the pH is over 7, in spite of the higher risk for deamidation [of the hGH]. When Kabi Pharmacia's product Genotropin® [registered trademark for Kabi Pharmacia's hGH] is reconstituted, a pH of 6.7 is obtained at a hGH concentration of 16 IU/ml. This pH is a compromise between a pH giving a totally clear solution (pH 8) and pH 6 giving a lower deamidation rate but somewhat more opalescence." (column 2, lines 50-64)

Continuing on, Castensson discloses that:

"Totally unexpected we have now found that solutions containing growth hormone in which citrate has been chosen as a buffer substance are more stable than those in which phosphate is the buffer." (column 3, lines 6-10)

Castensson teaches preferred liquid formulations of hGH with 2-40 mM citrate buffer at a pH of about 5.0 to 7.5 (column 3, lines 13-17). The liquid formulation of Castensson can contain carbohydrates (sucrose is a carbohydrate) and optionally a preservative (column 3, lines 23-28). McNamara teaches that chemical stability of liquid formulations of hGH are enhanced at a pH value of 6.0 or below (page 19, lines 9-10). Additionally, McNamara teaches that in the absence of PLURONIC® F68, aggregation and subsequent precipitation of hGH is maximal in the region of pH 5 to 6 (page 19, lines 21-22 and Figure 2) when the hGH liquid formulation is agitated, and that in the absence of PLURONIC® F68, less than 1% of hGH remained in solution after agitation, but 0.1 – 0.5% PLURONIC® F68 even at pH 5.6 prevented virtually all of the hGH from aggregating and precipitating out of solution (page 19, line 26 to page 20, line 8 and Figure 3). It would have been obvious to one of ordinary skill in the art at the time of the invention to make a liquid formulation of hGH comprising citrate buffer as explicitly suggested by Castensson and to lower the pH value of said formulation to 6.0 or below as explicitly disclosed by McNamara as long as the formulation comprised at least 0.1 – 0.5% PLURONIC® F68 to prevent the hGH from aggregating and precipitating out of solution, making it worthless as a pharmaceutical if agitated. Because the combination of the prior art references teach that citrate buffer and a pH at or below 6.0 in the presence, but not absence, of PLURONIC® F68 greatly improves the beneficial and desirable stability of liquid hGH formulations so that it is not ruined as a pharmaceutical composition upon agitation, the instant invention is rendered *prima facie* obvious.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is 571-272-0883. The examiner can normally be reached on Mondays through Fridays from 0930 to 1800.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at 571-272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/S. G./
Examiner, Art Unit 1649
Stephen Gucker
April 14, 2009

/Jeffrey Stucker/

Supervisory Patent Examiner, Art Unit 1649